REMARKS

Claims 1-5, 54, 56, 58-61, 63-70, 78-79, 82-83 and 104-107 are pending. Claim 54 has been amended to correct a minor clerical error. Support for the amending language may be found in originally filed claim 68. No new matter is added. In view of the following remarks, reconsideration and withdrawal of the rejections is requested.

Claims 1-5, 54, 56, 58-61, 63-70, 78-79, 82-83 and 104-107 have been rejected under 35 U.S.C. 112, first paragraph. The Office Action states that the claims contain subject matter which was not described in the specification in such a way as to convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

On page 2, the Office Action goes on to state that each recites a limitation of uroplakin (UPII) transcriptional regulatory element (TRE) that comprises specific nucleotide sequences as set forth in the Seqlist. The Examiner thus acknowledges that the structure of the claimed sequences is clearly described. On page 3, the Office Action further states a requirement that "desired urothelial cell-specific expression is obtained". He4nce, the Examiner further acknowledges that the function of the claimed sequences is also clearly described. Applicants agree with this assessment, and point out that the broadest claims are directed to a TRE comprising a nucleotide sequence selected from the group consisting of "nucleotides 2028 to 2239 of SEQ ID NO:1; nucleotides 1647 to 2239 of SEQ ID NO:1; nucleotides 1223 to 2239 of SEQ ID NO:1; nucleotides 1 to 2239 of SEQ ID NO:1; nucleotides 430 to 2239 of SEQ ID NO:1; nucleotides 2023-2239 of SEQ ID NO:1; nucleotides 3005 to 3592 of SEQ ID NO:2; and 2627 to 3592 of SEQ ID NO:2". Each TRE within the scope of the claims, therefore, has an absolute requirement that one of these eight, defined nucleotide sequences will be present.

The specification provides a number of examples of adenovirus vectors constructed with the claimed TRE fragments. For clarity, Applicants provide herein a detailed listing of adenovirus constructs that are described in the present application; with a lettering system to identify the presented claims UPII TREs.

	Sequence	Construct	Independent Claim	Support for urothelial cell specific activity
A	nucleotides 1 to 2239 of SEQ ID NO:1 **(human)**	CP657; CV876	4	Figs. 5 and 6
B	nucleotides 430 to 2239 of SEQ ID NO:1 **(human)**	CV882; CV884	5	Fig. 14 and page 117, lines 22-24 of the specification
C	nucleotides 1223 to 2239 of SEQ ID NO:1 **(human)**	CP656; CV875; CV832; CV833;	3	Figs. 5 and 6

		CV824; CV825		
D	nucleotides 1647 to 2239 of SEQ ID NO:1 **(human)**	CP663; CV822; CV823	2	Fig. 5
E	nucleotides 2028 to 2239 of SEQ ID NO:1 **(human)**	CP662	1	Fig. 5
F	nucleotides 3005 to 3592 of SEQ ID NO:2 **(mouse)**	CP618; CV826; CV827; CV830; CV831; CV818; CV819	64	Fig. 6
G	nucleotides 2627 to 3592 of SEQ ID NO:2 **(mouse)**	CP619; CV877; CV828; CV829; CV820; CV821	65	Fig. 6

Name	**Vector**	**Ad Vector**	**TRE**	**E1A TRE**	**TRE**
CV808	CP569	pBHG10		3.6 kb mUPII	
CV818	CP622	pBHG10	G	0.6 kb mUPII	
CV819	CP622	pBHGE3	G	0.6 kb mUPII	
CV820	CP623	pBHG10	F	1.0 kb mUPII	
CV821	CP623	pBHGE3	F	1.0 kb mUPII	
CV822	CP664	pBHG10	D	0.6 kb hUPII	
CV823	CP664	pBHGE3	D	0.6 kb mUPII	
CV824	CP665	pBHG10	C	1.0 kb hUPII	
CV825	CP665	pBHGE3	C	1.0 kb hUPII	
CV826	CP667	pBHG10	G	0.6 kb mUPII	C
CV827	CP667	pBHGE3	G	0.6 kb mUPII	C
CV828	CP669	pBHG10	F	1.0 kb mUPII	C
CV829	CP669	pBHGE3	C	1.0 kb hUPII	F
CV830	CP672	pBHG10	C	1.0 kb hUPII	G
CV831	CP672	pBHGE3	C	1.0 kb hUPII	G
CV832	CP673	pBHG10	C	1.0 kb hUPII	F
CV833	CP673	pBHGE3	C	1.0 kb hUPII	F

Figure 5 depicts the expression of a luciferase gene operably linked to a number of plasmids comprising UP TREs. Among these are CP648 (human uroplakin Ia TRE); CP649 (human uroplakin Ia TRE); CP662 (TRE fragment E); CP663 (TRE fragment D); CP656 (TRE fragment C); CP657 (TRE fragment A) and CP620 (SEQ ID NO:2, complete sequence). Applicants note that the

plasmids CP648 and CP649, as stated in Table 1, do not contain a UPII transcriptional regulatory element. A review of the expression of the 4 human uroplakins, UPIa, UPIb; UPII and UPIII is attached herewith to clarify this point (Lobban et al. (1998) AJP 153:1957-1967). Applicants also note that no claims are presently pending which claim the TRE that was used in CP620.

The vectors were tested in the following cell lines: HepG2, a hepatocellular carcinoma; LoVo, a colon carcinoma; PA-1, an ovary teratocarcinoma; SW780, a bladder cell carcinoma; SW1463, a rectal adenocarcinoma; and UM-UC3, a bladder cell carcinoma.

As stated in the specification (page 104, lines 9-14), constructs CP648 and CP649 showed no preferential expression in SW780 cells. However, CP618, CP620, CP662, CP663, CP656 and CP657 showed significant preferential expression in SW780 cells, indicating the presence of at least one urothelial cell-specific TRE in each of these constructs.

Therefore, based on the evidence presented in Figure 5, the UPIa promoters show little activity in any of the lines tested, but the CP662; CP663; CP656; CP657 and CP620 constructs all preferentially expressed in urothelial cells. These constructs, to reiterate, included the fragments A, B, D and E of the human UPII TRE.

Figure 6 also provides evidence of TRE activity, and tissue specificity. CP618; CP619; CP1066; CP656; CP657 and CP620 were assayed. All showed greater activity in SW780 than in other cells tested. . Also, the human TRE fragments A (CP657) and C (CP656) are preferentially expressed.

The murine UPII TRE provides for a biologically relevant effect (shown in Figure 11), where a bladder xenograft tumor is dramatically shrunk when treated with CV808.

The last of the figures in the application, Figure 14, compares the wild-type virus CV802 with CV882 and CV884, both of which utilize the UPII TRE B. It can be seen that the replication of CV882 in permissive cells (293, RT-4 and SW780) is comparable to wild-type, while it is substantially reduced in non-permissive cells (G361, LNCap, HBL-100, MKN1, PA-1 and primary cells).

Applicants respectfully submit that a set of clearly defined transcriptional regulatory elements are set forth in the specification and the claims. The elements are utilized in a large number of constructs, and varying configurations (see the above table). The data demonstrate that the TREs provide for expression of adenovirus genes essential for replication, as set forth in Claims 54, 56, 58-61, 63-70, 78-79, 82-83 and 104-107; and further are selectively expressed in bladder cells, as set forth in Claims 1-5.

The Office Action states that "a reasonably broad interpretation of the words 'uroplakin II TRE' in light of these teachings encompasses additional transcriptional regulatory elements (TREs) that are associated with the human and murine uroplakin II genes that respond under different conditions in urothelial cells (e.g. at different times during urothelial cell development) that are not present within SEQ ID NOs:1 or 2. The claims also reasonably encompass synthetic TREs that comprise additional elements derived from homologs of UPII obtained from other sources that are not identical to those described in the specification."

Applicants see no reason why the claimed subject matter should not encompass constructs where the provided – specifically defined and effective – TREs are combined with other regulatory elements, given that the claims recite structure and function clearly described in the specification. There is no question that Applicants have fulfilled the written description of the sequences set forth in the present claims. There is no ambiguity about what is meant by, for example, nucleotides 1647 to 2239 of SEQ ID NO:1. Nor is there any question that enhancers and promoters are widely used in the art, and that such use is enabled by well known assays and methods; including methods such as those provided in the examples of the present application.

It is well-known in the art that enhancers and promoters may be combined. Applicants have provided ample examples of the active fragments in SEQ ID NO1 and SEQ ID NO:2, and have shown the effectiveness of these fragments in cells and in animals. Whether a promoter is obtained from a virus, a synthetic promoter bought from a research supply house, or from the UPII sequence of another species is immaterial.

The Office Action states that "the rejected claims encompass embodiments where the claimed enhancer only comprises portions of the largest human and murine UPII TRE elements described in the instant specification (i.e. the 2.240 kb human UPII TRE described by SEQ ID NO:1 and the 3.592 murine UPII TRE described by SEQ ID NO:2). Because the rejected claims are drawn towards a UPII TRE comprising only portions of the sequences described in SEQ ID NO:1 or SEQ ID NO:2, the rejected claims encompass a very large number of potential TRE sequences."

Applicants submit that the claims are directed to very specific and carefully described portions of these sequences, which portions are shown to be active enhancers. The statement concerning "a very large number of potential TRE sequences" is not understood. The claims sequences are fully described, and their use is fully enabled. The number of possible nucleotide combinations that could be ligated to the ends does not detract from Applicants compliance with the requirements for written description.

The Office Action states that "the specification teaches only two sequences from different sources that considered to be TRE sequences associated with Uroplakin II genes". Applicants do not dispute this statement, but point out that, in fact, all of the claims specifically require one of the provided sequences to be present.

The Office Action states that "construct CP619, which comprises an intermediate fragment of 1.0 kb obtained from the human UPII genes showed little expression". Applicants respectfully draw the Examiner's attention to Figure 6. While this fragment may have low expression, it is, in fact, a positive enhancer element and it is preferentially expressed in bladder cells. Applicants have met their burden through the disclosure of the sequence and of the biological activity.

The Office Action states that "the specification does not provide a reliable basis for one to envision those embodiments comprising a specific subsequence of SEQ ID NO:1 or SEQ ID NOL2 in addition to the enhancer/promoter elements such that the synthetic construct will retain TRE activity."

Applicants respectfully submit that the burden for written description has been met by explicitly spelling out the sequences of the TREs to be used with the constructs of the invention; by the demonstrated use of such sequences in dozens of different combinations; and by the demonstrated biological activity of the sequences. These many teachings, in combination with the extensive guidelines provided by the specification and by the wide knowledge in the art with respect to the use of promoter and enhancer elements, more than provides what the law requires.

Finally, the Office Action states that "it is not unreasonable to limit the invention to that which has been described." Applicants respectfully submit that the presently claimed invention is fully described by the specification. In view of the above remarks, withdrawal of the rejection under 35 U.S.C. 112, first paragraph, is respectfully requested.

CONCLUSION

Applicants submit that all of the claims are now in condition for allowance, which action is requested. If the Examiner finds that a Telephone Conference would expedite the prosecution of this application, she is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any other fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-0815, order number CELL-016.

Respectfully submitted,

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